Urinary Albumin Excretion in Heart Failure with Preserved Ejection Fraction : An Interim Analysis of the CHART 2 Study

博士論文

Urinary Albumin Excretion in Heart Failure with Preserved Ejection Fraction - An Interim Analysis of the CHART 2 Study-

(収縮能が保持された心不全症例におけるアルブミン尿の測定意義に関する検討
－東北慢性心不全登録研究の結果から－)

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Abstract

***Aims*:** Heart failure with preserved ejection fraction (HFpEF;収縮能が保持された心不全) is characterized by multiple comorbidities, including chronic kidney disease (CKD;慢性腎臓病) that is one of prognostic risks for those patients. This study was performed to evaluate the prognostic value of albuminuria using urine dipstick test (UDT;尿試験紙), combined with estimated glomerular filtration rate (eGFR;推算糸球体濾過量), for mortality in HFpEF.

Methods and Results: I enrolled 2,465 consecutive patients with overt heart failure (HF;心不全) with left ventricular ejection fraction (LVEF;左室駆出率) ≥50% in our Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2;東北慢性心不全登録研究) study (NCT00418041). I defined Ótrace UDT as positive. I divided them into the following 4 groups based on eGFR and UDT; Group 1 (G1) (eGFR≥60, negative-UDT), G2 (eGFRÓ60, positive-UDT), G3 (eGFR<60, negative-UDT), and G4 (eGFR<60, positive-UDT). Totally, 29.5% of the HFpEF patients had positive-UDT. HFpEF patients with positive-UDT were characterized by higher B-type natriuretic peptide (BNP;B 型ナトリウム利尿ペプチド) levels and frequent histories of hypertension or diabetes. During a mean follow-up of 2.5 years, the HFpEF patients with positive-UDT showed higher mortality in each stratum of eGFR level. Multivariable adjusted Cox model showed that when compared with G1 (reference), the hazard ratio of all-cause death for G2, G3 and G4 was 2.44 (95% confidence interval 1.47-4.05, P=0.001), 1.43 (0.92-2.23, P=0.12), and 2.71 (1.72-4.27, P<0.001), respectively. Furthermore, the prognostic value of positive-UDT was robust for both cardiovascular and non-cardiovascular deaths.

Conclusions: These results indicate that measurement of albuminuria in addition to eGFR is useful for appropriate risk stratification in HFpEF patients.

Keywords: heart failure with preserved ejection fraction, albuminuria, urine dipstick test, estimated glomerular filtration rate

I. Introduction

The prevalence of patients with heart failure with preserved ejection fraction (HFpEF;収縮能が保持された心不全) has been rapidly increasing over the last 2 decades, whereas that of patients with HF with reduced ejection fraction (HFrEF;収縮能が低下した心不全) has been rather decreasing.[1] More than 50% of patients with the clinical syndrome of heart failure (HF;心不全) have a normal left ventricular ejection fraction (LVEF;.左室駆出率).[1] We have recently demonstrated that the prevalence of HFpEF has also increased in Japan in our HF cohort with 10,219 patients, named the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2;東北慢性心不全登録研究) Study.[2] The increase in the number of HFpEF patients may be explained by the fact that the Japanese society has been rapidly aging and thus the proportion of elderly HF patients has also been rapidly increasing.[3] Furthermore, the recent progress in reperfusion therapy has substantially contributed to preservation of LVEF after acute coronary events.[4, 5]

Although the survival of patients with HF improved during the last 2 decades among those with HFrEF, it did not improve among those with HFpEF.[1] Recent guidelines recommend the inclusion of objective evidence of diastolic dysfunction in diagnosing HFpEF,[6] however, due to the pathophysiological heterogeneity of HFpEF, it is difficult to establish the uniform definition of the disorder.[7] Furthermore, there is no authorized treatment guidelines for HFpEF, although the prognosis of patients with HFpEF is equally poor compared with HFrEF patients.[8] Diagnostic methods for diastolic dysfunction using echocardiography is clinically difficult. Therefore, simple diagnosing tools are needed for appropriate risk stratification in HFpEF patients.

HFpEF is typically characterized by multiple comorbidities, (e.g., anaemia, chronic kidney disease (CKD;慢性腎臓病), chronic obstructive lung disease (COPD;慢性肺気腫), hyperuricemia, cerebrovascular disease, malignant tumor).[9] Among these comorbidities, the prevalence of CKD is higher than other diseases.[9] Furthermore, CKD is associated with anaemia, hyperuricemia, and cerebrovascular disease. Therefore, CKD may be the most important comorbidities in HFpEF patients. Moreover, the effective treatment of CKD may

be more essential in HFpEF than in HFrEF.[10)]

Albuminuria is a well-known independent risk factor for mortality in the general population,[11)] hypertension,[12)] and diabetes,[13)] reflecting glomerular injury, systemic inflammation, and activation of renin-angiotensin system (RAS;レニンアンギオテンシン系). Therefore, the use of urine albumin to creatinine ratio (UACR;尿中アルブミンクレアチニン比) is currently emphasized to evaluate the severity of CKD.[14)] However, the severity of CKD is usually defined by reduced estimated glomerular filtration rate (eGFR;糸球体濾過量). In HF patients, it has reported that the prevalence of the patients with albuminuria (Ó30 mg/g) was about 30%.[15), 16)] Furthermore, HF patients with albuminuria (Ó30 mg/g) had poorer prognosis.[16)-19)] However, most of HF patients included in these studies were HFrEF.

The aim of this study was to evaluate the prognostic value of albuminuria using UDT combined with eGFR in HFpEF patients in our CHART-2 Study.

II. Methods

1. Population and inclusion criteria

Details of the design, purpose, and basic characteristics of the CHART-2 Study have been described previously (NCT00418041).[2] Briefly, eligible patients were aged Ó20 years with significant coronary artery disease or in the stage B, C or D defined by the Guidelines for the Diagnosis and Management of Heart Failure in Adults authorized by the American College of Cardiology Foundation (ACC;米国心臓病学会) / American Heart Association (AHA;米国心臓協会).[20] Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.[21] There were no other exclusion criteria in the study. The present study was approved by the local ethics committee in each participating hospital. Eligible patients were consecutively recruited after written informed consent was obtained. The CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients registered from the 24 participating hospitals. All data and events will be surveyed at least once a year until March 2013.

In the CHART-2 Study, LVEF was measured by echocardiography at the time of enrollment. In the present study, patients with LVEF≥50% were classified as having HFpEF, whereas those with LVEF<50% as having HFrEF.[1] The study flow diagram is shown in **Figure 1**. In the present study, I excluded the patients in stage B and those with severe valvular heart disease (VHD;弁膜症), congenital heart disease, pulmonary arterial hypertension, pericardial disease or on hemodialysis (**Figure 1**). Severe VHD was defined by the Guidelines for the management of patients with VHD authorized by the ACC/AHA.[22] Severe aortic valve stenosis was defined as follows; jet velocity was greater than 4.0m/second or valve area was less than 1.0cm^2. Severe aortic regurgitation was defined as follows; color doppler jet width was greater than 65% of left ventricular outflow tract or doppler vena contracta width was greater than 0.6cm. Severe mitral stenosis was defined as follows; mean pressure gradient was greater than 10mmHg or valve area was less than 1.0cm^2. Severe mitral regurgitation was defined as follows; vena contracta width was greater than or equal to 0.7cm or jet area was greater than 40% of left atrial area. I also excluded patients

who did not have UDT measurement. Therefore, 2,465 HFpEF patients were finally included in the present study (**Figure 1**).

2. Measurements of albuminuria

Albuminuria in the study population was qualitatively evaluated using UDT. Eight kinds of UDTs marketed by 5 medical corporations were used in the participating hospitals. The name of the corporation and percentage of patients were as follows; ARKLEY, Inc., Kyoto, Japan (39.4%), Eiken chemical Co. Ltd., Tokyo, Japan (26.2%), SIEMENS AG, Munich, Germany (21.9%), SYSMEX Corporation, Kobe, Japan (8.6%), Roche Diagnostics, Basel, Switzerland (3.6%) and unknown, 0.4%. All UDTs were calibrated to indicate 1+ qualitatively at urine protein concentration of ≥0.3 g/L. Detections of proteinuria on dipsticks of the 4 corporations (ARKELEY, Siemens AG, Eiken Chemical, and SYSMEX) were calibrated to indicate trace at ≥0.15 g/L, ≥0.1 g/L, ≥0.15 g/L, and ≥0.1g/L of proteinuria, respectively. Dipstick marketed by Roche Diagnostics did not originally indicate trace on proteinuria.

It has been reported that trace proteinuria evaluated by UDT could be a useful indicator of albuminuria (≥30 mg/g) in the subjects at high risk of cardiovascular disease.[23] Furthermore, a recent report denoted that trace UDT could identify urine albuminuria (≥30 mg/g) with high specificity and negative predictive value.[24] Thus, in the present study, I defined positive-UDT for proteinuria as ≥trace and the other as negative-UDT.

3. Renal function

Estimated GFR (ml/min/1.73m^2) was calculated using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient[25] at the time of enrollment as follows; GFR (ml/min per 1.73 m^2) = 186 × Creatinine$^{-1.154}$ × Age$^{-0.203}$ × 0.742 (if female) × 1.233. I defined reduced eGFR as <60 ml/min/1.73m^2 according to the guideline. [14]

4. Follow-up survey and study outcomes

I conducted the first survey of survival in August 2010 and the mean follow-up period of the

study population was 2.5±1.0 [SD] years. The outcomes of this study included all-cause death, cardiovascular death (CVD;心血管死), and non-cardiovascular death (NCVD;非心血管死). CVD was defined as deaths due to myocardial infarction, HF, cerebrovascular disease, aortic aneurysm rupture and sudden death. Deaths other than CVD were classified as NCVD. Mode of death was determined by the attending physician and was confirmed by one independent physician who was a member of the Tohoku Heart Failure Association.[2]

5. Statistical analysis

To evaluate the usefulness of UDT, I divided the 2,465 patients into the following 4 groups; Group 1 (G1) with normal eGFR with negative-UDT (N=1,043), G2 with normal eGFR with positive-UDT (N=342), G3 with reduced eGFR with negative-UDT (N=703), and G4 with reduced eGFR with positive-UDT (N=386) (**Figure 1**).

Comparisons of data among the 4 groups were performed by ANOVA test for continuous variables and by chi-square test for dichotomous variables. Continuous data were described as mean ± standard deviation (SD;標準偏差). Kaplan-Meier curves were plotted to evaluate the association between the results of UDT and all-cause death, CVD and NCVD.

I also constructed the following 4 Cox proportional hazard regression models; (a) unadjusted, (b) age- and sex- adjusted, (c) adjusted by the clinical status and comorbidities in addition to the model (b), and (d) fully adjusted including medical treatments. In the model (c), I included the following covariates that potentially influence the outcomes; age, sex, New York Heart Association class, history of admission for HF, body mass index, systolic blood pressure,[26)] heart rate,[27)] serum sodium, serum potassium, comorbidities[26)] (anemia defined as hemoglobin <12 g/dL in females and <13 g/dL in males, diabetes mellitus, hyperuricemia, atrial fibrillation, history of coronary artery disease, cerebrovascular disease, and malignant tumor) and brands of UDT. In the model (d), I included treatment (β-blocker, RAS inhibitors, calcium channel blockers, loop diuretics, and aldosterone antagonists) in addition to model (c). Finally, to determine the prognostic value of UDT in addition to eGFR, I constructed Cox proportional hazard models in patients with ≥60 or <60 of eGFR separately

including all covariates in the model (d) plus eGFR level.

All statistical analyses were performed using SPSS Statistics 19.0 (SPSS Inc. Chicago, Illinois, USA) and statistical significance was defined as a 2-sided P value less than 0.05.

III. Results

1. Baseline characteristics (Table 1)

Mean age was 69.6±11.7 years and male patients accounted for 68.2% in the study population. Coronary artery disease was observed in 52.1% and the mean LVEF and eGFR were 65.3±9.0% and 62.4±24.3 ml/min/1.73m^2, respectively. The prevalence of CKD patients, defined as eGFR<60 ml/min/1.73m^2, was 44.1% (N=1,089). The prevalence of the patients with positive-UDT was 29.5% (N=728). Furthermore, the prevalence of the patients with positive-UDT and with eGFR<60 was higher (35.4%, N=386) than that of the patients with positive-UDT and with eGFRÓ60 (24.9%, N=342). The patients with trace proteinuria accounted for the largest part of those with positive urine dipsticks. Male and older patients had higher prevalence of positive-UDT. Furthermore, the patients with eGFR<60 had severer positive urine dipstick results compared with those with eGFRÓ60.

The patients with reduced eGFR (G3 and G4) were characterized by older age, higher prevalence of HF admission. Furthermore, they had lower hemoglobin level, and were more likely to be taking furosemide, angiotensin II receptor blocker, and calcium channel blocker. The G1 and G3 patients had a negative-UDT. The patients in G1 who had normal eGFR were characterized by younger age and had the lowest B-type natriuretic peptide (BNP;B 型ナトリウム利尿ペプチド) level compared with other groups. The G3 patients who had reduced eGFR were characterized by more female compared with other groups. There were no differences in the prevalence of past history of coronary artery disease, atrial fibrillation, body mass index, LVEF or the usage rate of β–blocker among the 4 groups. However, some baseline characteristics of patients with positive-UDT were different from those with negative-UDT. Regardless of the existence of CKD, HFpEF patients with positive-UDT (G2 and G4) were characterized by higher prevalence of hypertension, diabetes mellitus, past history of HF admission, and cerebrovascular disease compared with those with negative-UDT. Furthermore, those with positive-UDT were associated with higher systolic blood pressure, elevated heart rate and higher BNP level.

2. Impact of positive urine dipstick test for all-cause death

During the mean follow-up period of 2.5±1.0 years, 213 patients (8.6%) died. Eight patients (0.3%) were lost to follow up. Figure 2A shows Kaplan-Meier survival curves for all-cause death. Groups with positive-UDT (G2 and G4) had poorer prognosis than those with negative-UDT (G1 and G3) within each stratum of eGFR (both P<0.001). Importantly, patients with positive-UDT and normal eGFR (G2) showed significantly poorer prognosis compared with those with negative-UDT and normal eGFR (G1).

Table 2 shows the results of multivariable Cox proportional hazard regression analysis for all-cause death (the upper portion). In the unadjusted model (a), as compared with G1 (reference), G2, G3 and G4 showed 202%, 239% and 500% increase in the risk for all-cause death, respectively (all P<0.001). In the model (c), as compared with G1, the hazard ratios (HRs) (95% CI) for all-cause death of G2, G3 and G4 were 2.60 (1.59-4.24), 1.47 (0.94-2.27), and 2.63 (1.67-4.13), respectively. Importantly, the significance of HRs for all-cause death in G2 and G4 remained robust after the adjustment by HF treatments in the model (d).

3. Impact of positive urine dipstick test for cardiovascular and non-cardiovascular death

Of the 213 deaths noted, 86 (40.4%) were due to cardiovascular cause. **Figure 2B** shows Kaplan-Meier survival curves for CVD. G2 showed significantly higher cardiovascular mortality compared with G1 (P<0.001). However, there was no significant difference in CVD between G3 and G4. **Table 2** shows the results of multivariable Cox proportional hazard regression analysis for CVD (the middle portion). In the fully adjusted model (d), as compared with G1 (reference), the HRs (95% CI) for CVD of G2, G3 and G4 were 3.58 (1.50-8.58), 2.34 (1.10-4.98), and 3.29 (1.48-7.31), respectively. Importantly, the significance of HRs for CVD in G2 and G4 remained robust in the model (b), (c) and (d).

NCVD were observed in 127 patients during the study period. Thirty nine patients (30.7%) died from malignant tumor. Furthermore, 34 patients (26.8%) died from infectious disease. **Figure 2C** shows Kaplan-Meier survival curves for NCVD. Groups with

positive-UDT had significantly higher NCVD than those with negative-UDT within each stratum of GFR (both P<0.001). **Table 2** shows the results of multivariable Cox proportional hazard regression analysis for NCVD (the lower portion). In the model (a), as compared with G1 (reference), the HRs (95% CI) for NCVD of G2, G3 and G4 were 2.75 (1.52-4.98), 2.41 (1.45-4.01) and 5.37 (3.26-8.83), respectively. However, in the models (b), (c) and (d), the HRs for NCVD in G3 was not significantly higher compared with those in G1 (**Table 2**). Again, the significance of HRs for NCVD in G2 and G4 remained robust in the model (b), (c) and (d).

4. Prognostic importance of urine dipstick test in addition to eGFR

About one third of the HFpEF patients in the present study had positive-UDT. **Figure 3** shows the results of Cox proportional hazard regression analysis for eGFR≥60 or <60 adjusted by the covariates including eGFR. In the HFpEF patients with eGFR≥60, as compared with G1, G2 showed 227%, 293% and 216% increase in the risk for all-cause death, CVD and NCVD, respectively (all P<0.001). In the HFpEF patients with eGFR<60, as compared with G3, G4 showed 174% and 212% increase in the risk for all-cause mortality and NCVD, respectively, whereas there was no significance for CV death.

IV. Discussion

The novel findings of the present study are the follows. First, about 30% of the HFpEF patients had positive-UDT. Second, the HFpEF patients with positive-UDT had significant higher mortality as compared with those with negative-UDT in each stratum of eGFR levels. Third, prognostic impact of positive-UDT was significantly enhanced after adjusted by the covariates including eGFR. These findings indicate that we need to perform UDT in addition to eGFR in all HFpEF patients for appropriate risk stratification.

1. Albuminuria as a marker of cardiorenal syndrome in HFpEF

Albuminuria is known as an independent risk factor for mortality in general population and in patients with hypertension or diabetes.[11)-13)] In HF patients, the prevalence of the patients with albuminuria (Ó30mg/g) was about 30%.[15),16)] Furthermore, HF patients with albuminuria (Ó30mg/g) had poorer prognosis independent of diabetes, hypertension, or renal function.[16)-19)] Anand et al. reported that proteinuria was associated with abnormal physical findings and clinical indicators of volume overload, which suggests that a possible pathogenic role of increased intravascular volume.[17)] Furthermore, RAS-activation and inflammation have been suggested to play causal roles in increasing albuminuria.[19)] Therefore, HF patients with albuminuria (Ó30mg/g) may have higher RAS-activity compared with those without albuminuria. However, most of HF patients included in these studies were HFrEF.

To our knowledge, this is the first report describing the relationship between HFpEF and albuminuria using UDT. In HFpEF patients, the prevalence of albuminuria (Ó30mg/g) was almost similar to that of HFrEF. Furthermore, HFpEF patients with positive-UDT had significant poorer prognosis. The mechanisms linking albuminuria and HFpEF remain unknown. However, there may not be large difference between HFrEF and HFpEF about the mechanism of elevated albuminuria.

CKD is a frequent complication of HF and this close association has been called the cardiorenal syndrome (CRS).[28)] Both CKD and HF are associated with an increased activity of sympathetic nervous system and RAS-activation, oxidative stress, and inflammation.[28)]

Therefore, we usually pay attention to renal function in HF patients. Compared with HFrEF patients, HFpEF patients were considered to have smaller RAS-activity.[29] However, according to the pathophysiology of elevated albuminuria in HF patients, HFpEF patients with albuminuria (Ó30mg/g) may have higher RAS-activity than those with normal albuminuria. Therefore, the linkage between heart and kidney in HFpEF patients with albuminuria (Ó30mg/g) may be larger than those in HFpEF patients without normal albuminuria. So, the measurement albuminuria is essential to evaluate CRS in addition to eGFR in all HF patients.

2. Benefit of the combination of eGFR and UDT in predicting the prognosis

Although guidelines for the classification and staging of CKD are based on eGFR, the use of UACR is currently emphasized for the assessment of CKD.[14] However, most physicians may consider that albuminuria measurement is not so convenient even in HF patients. In most clinical settings, eGFR is calculated by age, sex and serum creatinine.[25] HFpEF patients usually tend to be older and female.[1] Therefore, some HFpEF patients may indicate eGFR<60 without significant renal damage. Indeed, in the present study, the HFpEF patients in G3 were older and more female as compared with other groups. The present result shows that HFpEF patients with negative-UDT tend to have better prognosis than those with positive-UDT.

UDT has been widely used as an initial screening method for evaluation of proteinuria on the basis of low cost and the ability to provide rapid point-of-care information to clinicians and patients.[24] Furthermore, UDT is most sensitive to albumin but is less sensitive to globulins and secreted proteins.[24] Konta et al. has reported the significant usefulness of ≥trace UDT to predict albuminuria (≥30 mg/g) in the general population.[23] Furthermore, the negative predictive value of UDT for identification of albuminuria (≥30 mg/g) was higher than the threshold of ≥1+.[23] Thus, in the present study, I defined positive-UDT for albuminuria when the analysis showed ≥trace. Albuminuria (≥30 mg/g) is observed in approximately one third of HF patients.[15),16] In the present study, the prevalence of patients with positive-UDT with normal eGFR and those with reduced GFR was 24.9% and

35.4%, respectively. Thus, our findings indicate that positive-UDT is useful for detection of albuminuria and could be a reasonable surrogate of UACR measurement in HFpEF patients.

In HFpEF patients with eGFR Ó60, those with positive-UDT showed about twice higher mortality than those with negative-UDT. Furthermore, in the HFpEF patients with eGFR<60, those with positive UDT also showed significantly higher mortality compared with those with negative-UDT. This result indicates that we should perform UDT in addition to eGFR evaluation in HFpEF patients regardless of eGFR.

3. Implications of positive urine dipstick test in HFpEF

The reason of the poorer prognosis of HFpEF patients with positive-UDT remains to be fully clarified. In the present study, the HFpEF patients with positive-UDT were characterized by higher BNP level, suggesting that venous filling pressure is significantly increased. Venous congestion could cause proteinuria in dogs,[30] implicating that elevated venous pressure may be associated with the development of albuminuria. Furthermore, albuminuria may attenuate the effect of furosemide because filtered albumin may bind furosemide in the tubular fluid and impair the interaction with the luminal co-transporting proteins.[31] Resistance to diuretics may deteriorate venous congestion status with a resultant vicious cycle of albumin excretion into urine. Thus, the therapeutic strategy for reducing albuminuria is important in HFpEF patients.

In the present study, 40% of deaths were caused by cardiovascular events. Zile et al. also reported that 60% of deaths in HFpEF patients were CVD.[32] Albuminuria reflects glomerular injury, systemic inflammation and endothelial dysfunction that lead to cardiovascular events.[16] Furthermore, albuminuria has been associated with changes in coagulation factors.[33] In the present study, the rate of CVD was relatively low; however, positive-UDT could predict CVD in HFpEF patients, especially in those with normal eGFR. In HFpEF patients with eGFR<60, the patients with positive-UDT showed no significant difference in the development on CVD compared with those with negative-UDT. This result indicated that the influence of eGFR decline on CVD may be larger than albuminuria in the patients with eGFR<60. However, Perkins et al. reported that cases of early eGFR decline

occurred in 9% of the normal albuminuria group and 31% of the albuminuria (Ó30mg/g) group in diabetes patients.[34] Therefore, in the follow-up period, there may be a considerable eGFR decline in the patients with positive-UDT compared with those with negative-UDT that leads to poor outcome. So, we need to perform UDT in addition to eGFR even in HFpEF patients with eGFR<60.

In the present study, positive-UDT was also associated with increased NCVD, a consistent finding with the previous report by Hillege et al.[33] Approximately one third of the NCVD were due to malignant tumors in the present study. Although the underlying mechanisms remain to be elucidated, patients with advanced malignant tumor have a significantly higher urinary albumin excretion rate than those with localized disease.[35]

In the present study, the remaining one third of NCVD was due to infectious diseases. HFpEF patients with albuminuria tended to accompany with cerebrovascular disease that lead to impaired activities of daily living (**Table 1**). Such patients are particularly at high risk of infectious disease. The present results also indicate that the prevention for infectious diseases and cerebrovascular disease are important to reduce the mortality of HFpEF patients.

4. Treatment strategy of HFpEF patients with positive urine dipstick test

The underlying mechanisms of the close relationship between the heart and the kidney include inflammation and activated RAS and/or sympathetic nervous system.[16] Importantly, these mechanisms are also involved in the pathogenesis of albuminuria.[16] It was reported that RAS inhibitors cause a significant decrease in albuminuria and a trend of decrease in cardiovascular events in patients with hypertension, left ventricular hypertrophy and diabetes.[36] On the other hand, RAS inhibition in HFpEF is not associated with consistent reduction in HF admission nor mortality.[29] The overall failure of RAS inhibitors to improve morbidity and mortality of HFpEF patients suggest a relatively smaller contribution of neurohumoral activation on HF progression as compared with HFrEF patients.[29] However, the HFpEF patients with positive-UDT may have higher RAS activity than those with negative-UDT. It was reported that telmisartan treatment was associated with an increased risk of adverse renal events in patients without albuminuria, whereas it tended to improve

outcomes of patients with albuminuria.[37] Thus, baseline albuminuria level may be an important factor when selecting patients for the treatment with RAS inhibitors.[38] Again, the importance of UDT should be emphasized before we start to use RAS inhibitors for HFpEF patients.

We need to consider other therapeutic options for HFpEF patients in addition to RAS inhibitors. Carvedilol, a beta blocker with antioxidant effects, exerts a greater therapeutic effects for albuminuria as compared with metoprolol.[39] Spironolactone, an aldosterone antagonist, also exerts a beneficial effect for albuminuria.[39] Thus, standard therapy for HF may be needed to improve long-term prognosis of HFpEF patients with positive-UDT.

5. Study limitations

Several limitations should be mentioned for the present study. First, I had no information other than LVEF on left ventricular function, and it therefore remains unknown whether the study population had objective evidence of diastolic dysfunction recommended by the recent guidelines in the diagnosis of HFpEF.[6-8] Second, in the present study, UDTs from 5 different companies were used in the participating hospitals. Four dipsticks were calibrated to indicate trace at $\geq$0.1 g/L or $\geq$0.15 g/L of proteinuria and 1 dipstick did not indicate trace originally. Furthermore, sensitivity and specificity for detecting albuminuria may be different among these dipsticks. However, multivariate analyses including all covariates with the UDT brands clearly showed the significant prognostic impact of positive-UDT in HFpEF patients. Third, the present results were analyzed by data collected at the entry of subjects and I did not take into consideration the possible changes in UDT during the follow-up period. Fourth, the primary design of the present study did not cover chronic lung disease, which has been recognized as one of the important prognostic factors of HFpEF.[9] Finally, since the CHART-2 study is an observational study, the present results need to be carefully interpreted especially when the effects of treatment are evaluated.

V. Conclusions

The present results demonstrate that albuminuria predicts the mortality of HFpEF patients in

each stratum of eGFR levels, suggesting its usefulness for appropriate risk stratification in those patients.

Acknowledgments

I thank all members of the Tohoku Heart Failure Society and staffs of the department of evidence-based cardiovascular medicine for their kind contributions. This study was supported by Grants-in-Aid from a Research Grant from the Ministry of Health, Labour, and Welfare (H.S. and N.S.), and a Research Grant from the Ministry of Education, Culture, Sports, Science, and Technology (N.S.), Japan.

Conflict of interest

None.

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Figure Legends

Figure 1. Study flow diagram.

Figure 2. Kaplan-Meier survival curves for all cause death (**A**), cardiovascular death (**B**), and non-cardiovascular death (**C**). The 4 groups were categorized based on eGFR and urine dipstick test (UDT); Group 1 (G1) (eGFR≥60, negative-UDT), G2 (eGFRÓ60, positive-UDT), G3 (eGFR<60, negative-UDT) and G4 (eGFR<60, positive-UDT).

Figure 3. Hazard ratios for all-cause death, cardiovascular death, and non-cardiovascular death after adjustment by multiple covariates including eGFR. (**A**) eGFRÓ60 (G2 vs. G1), (**B**) eGFR<60 (G4 vs. G3). HR, hazard ratio; 95%CI, 95% confidence interval.

Table 1. Baseline characteristics of the study patients.

	Group 1 N = 1034	**Group 2 N = 342**	**Group 3 N = 703**	**Group 4 N = 386**	
↓ eGFR	**-**	**-**	**+**	**+**	
Dipstick	**negative**	**positive**	**negative**	**positive**	**P value**
Age (yrs.)	66.2 ± 11.8	67.3 ± 12.4	73.9 ± 9.5	73.1 ± 10.8	< 0.001
Male (%)	69.4	76.3	62.2	68.9	< 0.001
History of admission for HF (%)	38.8	48.4	53.1	56.1	< 0.001
Comorbidities (%)					
Hypertension	70.8	75.6	76.4	85.1	< 0.001
Diabetes	22.0	29.2	21.6	33.2	< 0.001
Hyperuricemia	26.0	26.6	55.0	60.1	< 0.001
Atrial fibrillation	27.8	33.0	35.2	31.7	0.05
Coronary artery disease	52.2	48.5	51.1	56.7	0.15
Cerebrovascular disease	12.2	16.7	19.8	21.5	< 0.001
Malignant tumor	9.5	12.0	13.1	13.2	0.10
Clinical status					
NYHA class 3 and 4 (%)	6.3	5.6	12.1	11.5	< 0.001
Body mass index (kg/m^2)	23.9 ± 4.5	23.9 ± 5.6	23.7 ± 4.7	23.7 ± 4.4	0.87
Systolic blood pressure (mmHg)	127.4 ± 17.1	131.8 ± 18.9	127.6 ± 19.2	133.4 ± 20.1	< 0.001
Diastolic blood pressure (mmHg)	74.1 ± 11.1	75.1 ± 12.6	71.7 ± 12.3	72.5 ± 12.1	< 0.001
Heart rate (beat/min)	70.9 ± 13.9	73.6 ± 15.8	70.7 ± 13.8	72.5 ± 12.1	0.003
Measurement					
LVEF (%)	65.2 ± 9.0	65.0 ± 9.4	65.7 ± 9.1	64.8 ± 8.5	0.40
LVDd (mm)	48.8 ± 6.9	49.0 ± 7.3	48.7 ± 7.5	49.1 ± 7.4	0.74
Hemoglobin (g/dL)	13.7 ± 1.7	13.8 ± 2.4	12.7 ± 2.0	12.2 ± 2.1	< 0.001
Blood urea nitrogen (mg/dL)	15.3 ± 4.2	15.5 ± 4.1	22.3 ± 8.8	26.2 ± 12.0	< 0.001

Serum sodium (mEq/L)	141.0 ± 2.6	140.9 ± 2.9	140.9 ± 2.8	141.2 ± 3.2	0.40
Serum potassium (mEq/L)	4.3 ± 0.4	4.2 ± 0.4	4.5 ± 0.5	4.4 ± 0.5	< 0.001
Serum albumin (g/dL)	4.2 ± 0.4	4.1 ± 0.5	4.1 ± 0.4	3.9 ± 0.6	< 0.001
GFR (ml/min/1.73 m^2)	76.5 ± 29.6	77.3 ± 15.7	45.6 ± 11.0	40.5 ± 12.9	< 0.001
Brain natriuretic peptide (pg/mL)	94.5 ± 118.1	134.9 ± 162.2	159.7 ± 176.7	242.4 ± 467.3	< 0.001
Medications					
ACE inhibitor (%)	40.9	50.3	43.5	39.4	0.01
ARB (%)	30.7	27.2	37.4	40.9	< 0.001
Beta blocker (%)	43.0	49.7	44.4	44.8	0.20
Calcium channel blocker (%)	41.8	48.0	48.4	59.3	0.03
Loop diuretics (%)	32.8	34.8	52.3	52.8	< 0.001
Furosemide dose (mg)	6.8 ± 13.7	8.7 ± 17.0	12.6 ± 19.2	13.4 ± 19.1	< 0.001
Aldosterone inhibitor (%)	14.1	16.1	23.8	17.4	< 0.001
Statin (%)	40.1	35.7	41.8	43.3	0.17
Outcome					
Follow-up period (yrs.)	2.5 ± 1.0	2.3 ± 1.0	2.5 ± 1.0	2.3 ± 1.1	< 0.001
All-cause death (%)	3.3	9.0	11.0	18.1	< 0.001
Cardiovascular death (%)	1.0	3.2	5.5	6.7	< 0.001

HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. Numerical data are shown as mean ± standard deviation.

Table 2. Cox proportional hazard model for all-cause death, cardiovascular death, and non-cardiovascular death

HR Categories	eGFR <60	Dipstick	No. of events (%)	No. of events /100 person /year	(a) Unadjusted			(b) Age- and Sex- adjusted			(c) All baseline adjusted			(d) Fully adjusted including treatment		
					HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
All-cause death							< 0.001			< 0.001			< 0.001			< 0.001
Group 1 (reference)	-	-	34 (3.3)	1.5	1.00			1.00			1.00			1.00		
Group 2	-	+	31 (9.0)	4.0	3.02	1.85 - 4.91	< 0.001	2.60	1.59 - 4.24	< 0.001	2.57	1.56 - 4.25	< 0.001	2.44	1.47 - 4.05	0.001
Group 3	+	-	78 (11.0)	4.4	3.39	2.26 - 5.07	< 0.001	2.07	1.37 - 3.13	0.001	1.46	0.94 - 2.27	0.09	1.43	0.92 - 2.23	0.12
Group 4	+	+	70 (18.1)	7.9	6.00	3.98 - 9.04	< 0.001	3.78	2.48 - 5.74	< 0.001	2.63	1.67 - 4.13	< 0.001	2.71	1.72 - 4.27	< 0.001
Cardiovascular death							< 0.001			< 0.001			< 0.001			< 0.001
Group 1 (reference)	-	-	10 (1.0)	0.4	1.00			1.00			1.00			1.00		
Group 2	-	+	11 (3.2)	1.4	3.65	1.55 - 8.59	0.003	3.30	1.40 - 7.80	0.006	3.66	1.53 - 8.72	0.003	3.58	1.50 - 8.58	0.004
Group 3	+	-	39 (5.5)	2.2	5.72	2.85 - 11.45	< 0.001	3.68	1.80 - 7.49	< 0.001	2.34	1.13 - 5.09	0.023	2.34	1.10 - 4.98	0.03
Group 4	+	+	26 (6.7)	2.9	7.53	3.63 - 15.63	< 0.001	5.06	2.40 - 10.60	< 0.001	3.25	1.47 - 7.18	0.004	3.29	1.48 - 7.31	0.003
Non-cardiovascular death							< 0.001			< 0.001			< 0.001			< 0.001
Group 1 (reference)	-	-	24 (2.3)	1.1	1.00			1.00			1.00			1.00		
Group 2	-	+	20 (5.8)	2.6	2.75	1.52 - 4.98	0.001	2.29	1.26 - 4.16	0.007	2.03	1.09 - 3.78	0.026	1.89	1.01 - 3.54	0.048
Group 3	+	-	39 (5.5)	2.2	2.41	1.45 - 4.01	0.001	1.42	0.84 - 2.40	0.18	1.06	0.61 - 1.86	0.83	1.05	0.60 - 1.84	0.88
Group 4	+	+	44 (11.4)	5.0	5.37	3.26 - 8.83	< 0.001	3.24	1.95 - 5.40	< 0.001	2.41	1.39 - 4.19	0.002	2.51	1.44 - 4.37	0.001

HR, hazard ratio; CI, confidence interval. In the model (・)・ I adjusted the model by age, sex, and clinical status (NYHA class, systolic blood pressure, heart rate, body mass index, LVEF), serum sodium, serum potassium, history of admission for heart failure, and comorbidities (diabetes, hyperuricemia, anemia, coronary artery disease, cerebrovascular disease, atrial fibrillation, malignant tumor) and five urine dipstick test brands. In the model (d), in addition to the model (c), I adjusted the model by treatment (beta blocker, angiotensin converting enzyme blocker, angiotensin II receptor blocker, calcium channel blocker, loop diuretics, aldosterone antagonist).

Figure 1.

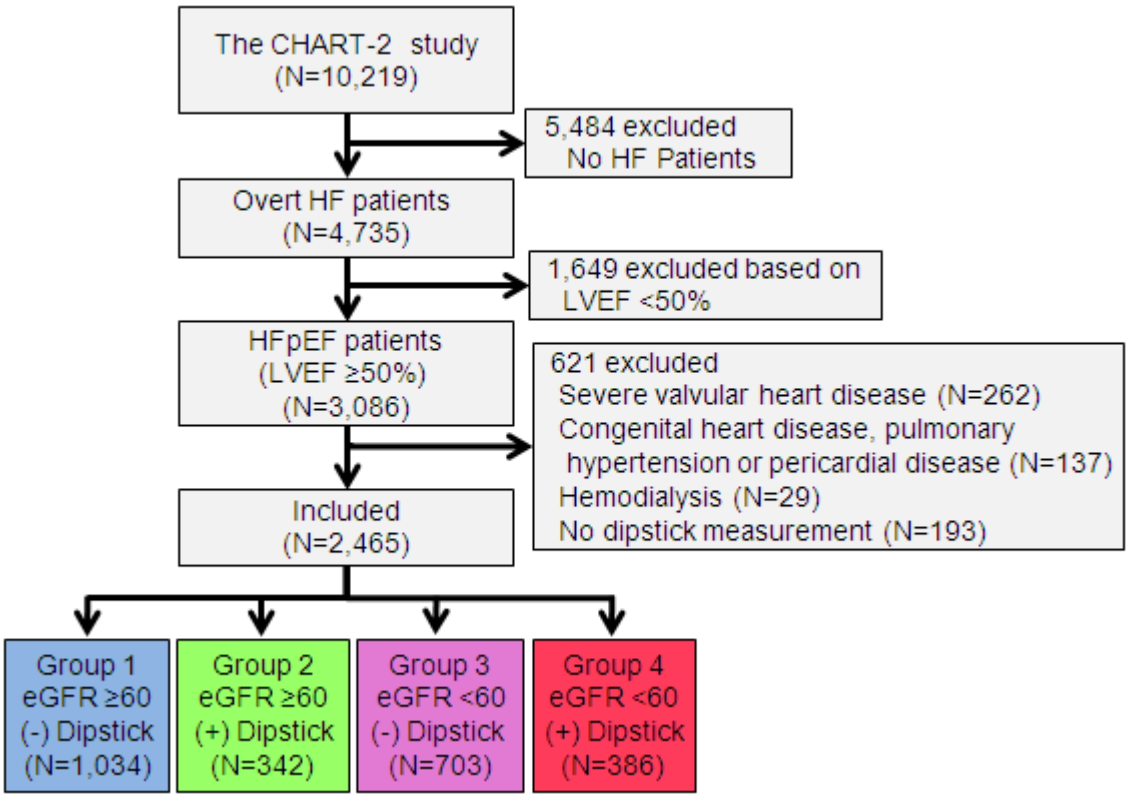
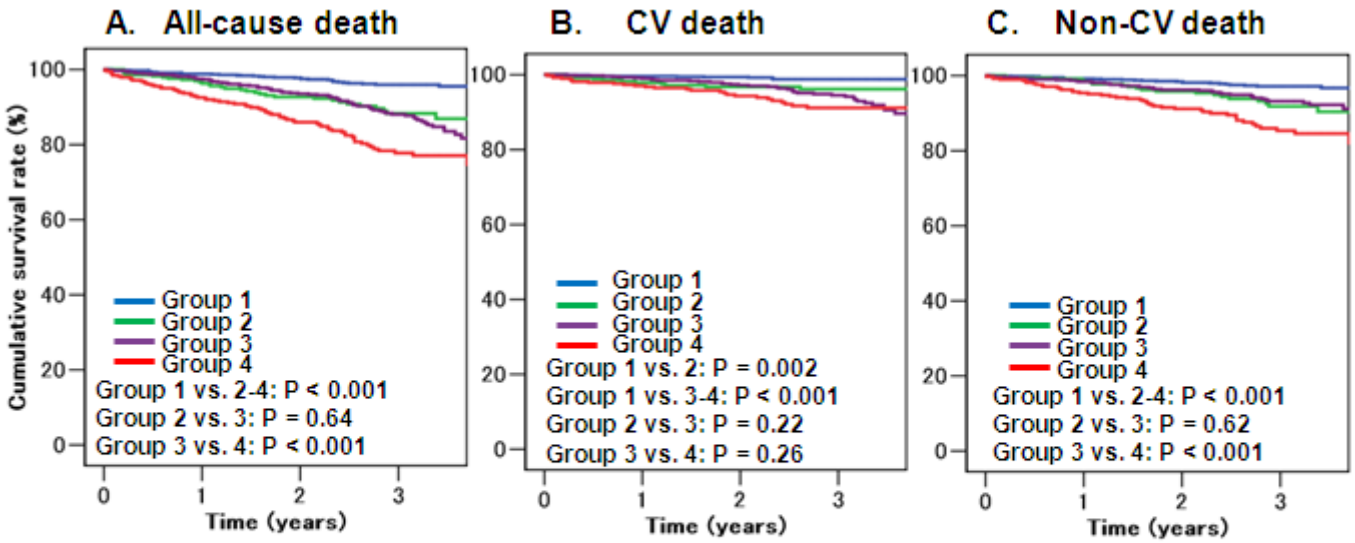
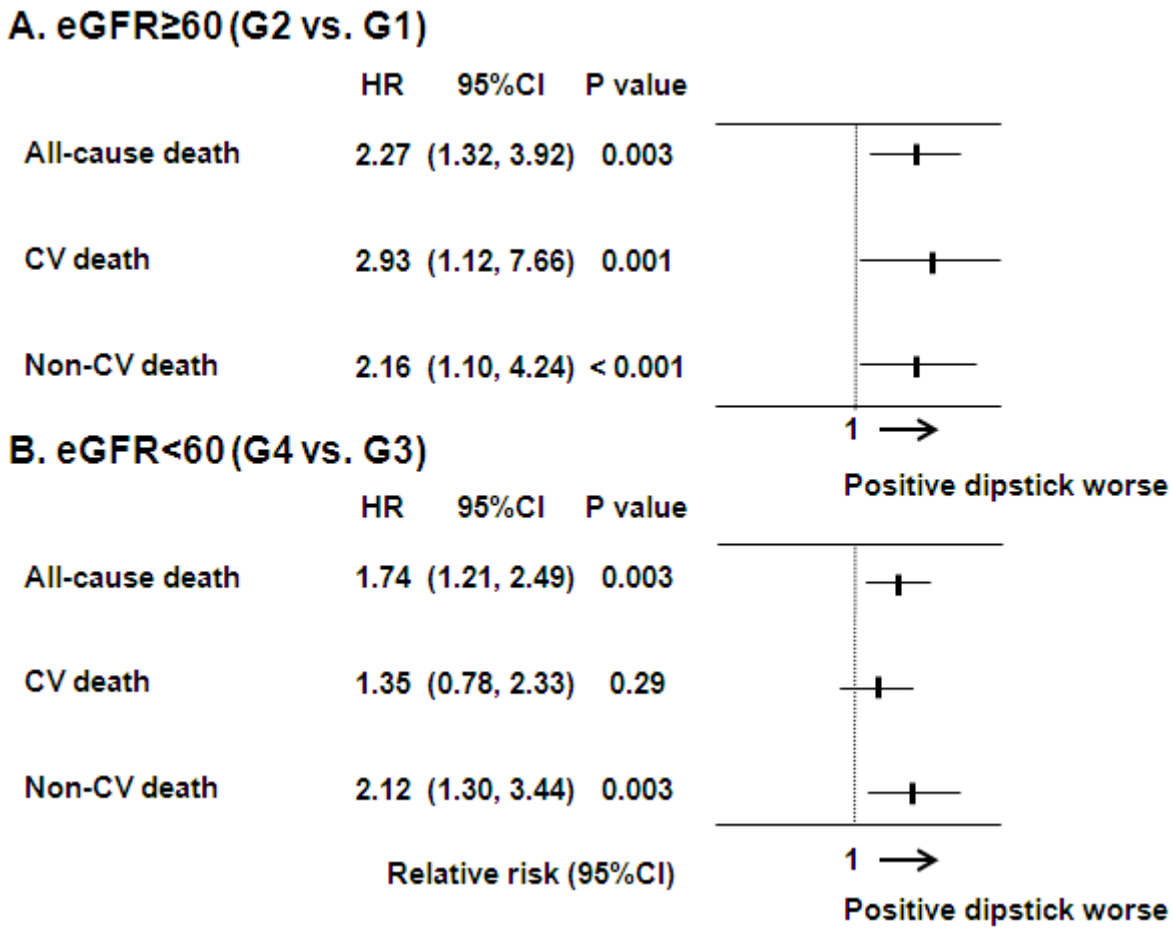

The CHART-2 study
(N=10,219)
5,484 excluded
No HF Patients
Overt HF patients
(N=4,735)
1,649 excluded based on
LVEF <50%
HFpEF patients
(LVEF ≥50%)
(N=3,086)
621 excluded
Severe valvular heart disease (N=262)
Congenital heart disease, pulmonary
hypertension or pericardial disease (N=137)
Hemodialysis (N=29)
No dipstick measurement (N=193)
Included
(N=2,465)
Group 1
eGFR ≥60
(-) Dipstick
(N=1,034)
Group 2
eGFR ≥60
(+) Dipstick
(N=342)
Group 3
eGFR <60
(-) Dipstick
(N=703)
Group 4
eGFR <60
(+) Dipstick
(N=386)

Figure 2.



G1	1034	944	755	426	1034	944	755	426	1034	944	755	426
G2	342	289	216	119	342	289	216	119	342	289	216	119
G3	703	641	495	276	703	641	495	276	703	641	495	276
G4	386	331	243	128	386	331	243	128	386	331	243	128

Figure 3.


A. eGFR≥60 (G2 vs. G1)
HR 95%CI P value
All-cause death 2.27 (1.32, 3.92) 0.003
CV death 2.93 (1.12, 7.66) 0.001
Non-CV death 2.16 (1.10, 4.24) < 0.001
1
Positive dipstick worse
B. eGFR<60 (G4 vs. G3)
HR 95%CI P value
All-cause death 1.74 (1.21, 2.49) 0.003
CV death 1.35 (0.78, 2.33) 0.29
Non-CV death 2.12 (1.30, 3.44) 0.003
Relative risk (95%CI)
1
Positive dipstick worse